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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,281	10/13/2000	Hyun Kim	GI 5387	9127

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EXAMINER	
HARLE, JENNIFER I	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 05/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/687,281	KIM ET AL.	
	Examiner	Art Unit	
	Jennifer I. Harle	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14-16 and 22-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,14-16 and 22-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01-19-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 14-, 16, and 22-78 are pending in Applicants' Request for Continuing Application.

Information Disclosure Statement

2. Applicants submitted an IDS with the RCE, it is noted that one of the Patent Number submitted did not correspond in subject matter, inventor or patent date. Upon further search, the examiner determined that the patent number to which Applicants were referring was 5,510,121 instead of 5,540, 121. If this is incorrect, the examiner requests that Applicant notify the examiner in the next response.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Rhee, et al. (US 5,510,121).

Rhee discloses pharmaceutically acceptable, non-immunogenic compositions, which are formed by covalently binding glucosaminoglycans or derivatives, including hyaluronic acid, thereof to hydrophilic synthetic polymers via specific types of chemical bonds to provide biocompatible conjugates. Abstract. These glucosaminoglycans or derivatives thereof, including hyaluronic acid, can be coupled with the synthetic polymer, PEG (liquid pore former), via different kinds of covalent compositions including ester and ester bonds. Col. 6, lines 4-39, cols. 9-10, lines 60-59, cols. 11-12, lines 63-51. Thus, Rhee clearly

discloses the use of hyaluronic acid esters and PEG in corresponding compositions. Rhee further discloses that the conjugates can be used as injectable drug or cell delivery systems. Col. 5, lines 32-34, col. 10, lines 6-7. Moreover, Rhee discloses that the compositions can contain biologically active proteins exemplified as growth factors or cytokines are further taught to include bone morphongenic protein (BMP) and osteogenic factors, which are especially suitable. Abstract, col. 12, lines 7-18, claims 1-3. Rhee further discloses that the compositions comprise conjugates with ceramic particles, preferable hydroxyapatie or tricalcium phosphate (TCP), are particularly useful for the repair of stress-beraing bone due to its high tensile strength. Col. 11. Thus, Rhee discloses an injectable composition which contains hyaluronic acid ester, PEG, TCP said composition further contains bone morphogenic factors or osteogenic factors.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 14-16, and 22-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhee, et al. (US 5,510,121) in view of Radomsky (WO 97/32591) and/or Celeste, et al. (5,658,882) in view of Vercruysse and Prestwich, Hyaluronate Derivatives in Drug Deliver, Critical Reviews in Therapeutic Drug Carrier Systems, 1998, 515(5), pp. 519-555 and/or Campoccia, et al., Semisynthetic Resorbable Materials from Hyaluronan Esterification,

Biomaterials, 1998, 19, 2101-2127 in view of Valle (US 5,336,767) in view of Radomsky (US 5,942,499).

Rhee discloses as set forth above.

Additionally, the use of hyaluronic acid as injectable matrix material was well known, and hyaluronic acid esters and their possible advantages as compared to hyaluronic acid itself in view of properties which are relevant for drug delivery were discussed in document of the state of the art. Radomsky discloses a bone growth-promoting composition comprising hyaluronic acid and a growth factor. Abstract. Radomsky explicitly discloses the proteins BMP-1 to BMP-12, GDF-1 to GDF-12 as suitable growth factor and notes that others are mentioned. See Pg. 2, line 2. Radomsky further discloses that the solution containing hyaluronic acid and growth factor should have a viscosity which allows for injection of the composition through a syring or catheter. Pg. 3. Moreover, Radomsky discloses that it is desirable that the composition has a residence time at the active site of 3 to 30 days. Pg. 3, lines 22-28. Finally, Radomsky lists suitable applications for a corresponding composition, which include administration in connection with bone fracture and includes other pathological defectes connected with bone growth or bone lesions.

Celeste discloses compositions containing a bone morphongenetic protein (explicitly mentioned are BMP-12, BMP-13 or MP52) together with suitable carriet materials, such compostions being suitable for administration via injection. Abstract, cols. 1-3, col. 12, lines 51-57. Celeste additionally discloses that the compositions can include a suitable matrix and/or sequestering agent as a carrier, i.e. the sequestering agent may be a substance, which aids an ease of administration through injection or other means, or may

slow the migration of protein from the site of the application and includes hyaluronic acid or derived therefrom. Col. 13, lines 9-53. Thus, Celeste discloses compositions which are suitable for injection and comprise an osteogenic protein together with hyaluroinic acid or its derivatives.

Thus, as set forth in Applicants Specification, it is pointed out that a multitude of patents relating to the use of injectable osteogenic proteins, i.e. BMP 2, 4-12, useful with injectable carriers made in accordance with the subject invention had already been well known in the art and before the filing date. See Specification, pp. 1-2 and 4-5. Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention that the combinations of hyaluronic acid derivatives, i.e. esters, and osteogenic proteins were advantageous and furthermore that injectable forms could be produced and used as drug delivery devices for both the hyaluronic acid ester and the osteogenic protein.

Vercruysse discloses that sodium hyaluronate and hyaluronic acid are collectively determined as hyaluronan, abbreviated as HA. Pg. 514, first paragraph. Vercruysse additionally discloses that unmodified HA has found important applications in drug delivery and surgery and that the physiochemical properties of HA can be adapted to the desired application by chemical modification and furthermore it can be gathered that HA-drug hydrogels may be used to localize a slow release formulation at a specific site in the body. Pp. 514-515. Vercruysse further discloses the production and possible uses of chemically modified hyaluronic acids for drug delivery and in the Table shown on page 516 specifies derivatives of HA as e.g. HA ester derivatives for the use in drug delivery and their availability from co-patentee Fidia (Advanced Biopolymers S.R.L.). Vercuysse discloses on page 519 the esterification of the carboxylic acid groups of HA and in Table 2

on page 522 HYAFF11px (px refers to the percentage of carboxylic functions modified) HYAFF11, which is the being the preferred compound of the instant application and used in the Examples is discussed as well as HYAFF11p50, HYAFFp75. Vercuysse also discusses the injection into mice of Hylan gel slurry and its evaluation, as well as microspheres prepared from HA esters for delivery devices for several growth factors and the various effects of delivery. Pg. 533

Campoccia discloses hyaluronic acid and partially or completely esterified forms of this natural polymer. See entire article, especially pg. 2103 (referring to ester formation and the properties of the obtained hyaluronic acid ester are described. Campoccia discloses that Hyaff11 is one of the most characterized Hyaff polymers from both the physicochemical and biological viewpoints and is useful in understanding the effect that changine two variables, the type of ester and the percentabe of esterification have on molecular properties, i.e. the extent of molecular modification modulates the soluble and viscous nature of purified hyaluronan in aqueous solution and has proved to have profound effects on the interaction of hyaluronan with water (the higher the percentage of esterification of hyaluronan, the lower is solubility in water; the total benzyl ester HYAFF 11 showed only slight hydration when placed in buffered phosphate saline solution while 75% hyaluronan benzyl esters HYAFF11p75 hydration was even greater). Pg. 2103. Campoccia also discloses degredagtion profiles between HYAFF11 (slower degredation, 2-3 months, more stable) and hydrated HYAFF11p75 (1-2 weeks) probably because partial esters are more flexible and hydrated than more completed esterified esters in which the hydrophobic patches make the polymer chain network more rigid and stable. Campoccia further discloses that derivatives with as little as 25% esterification. Campoccia

additionally discloses the possibility of using hyaluronic acid ester as a carrier and/or matrix for drug delivery

Thus it would have been obvious to one of ordinary skill in the art to combine either Vercuysse and/or Campoccia to use hyaluronic acid esters from 0% t0 100% and that all applications for which hyaluronic acid itself had been used appear to the skilled artisan as suitable biles of application for the corresponding ester so that the use of delivery of osteogenic proteins, including the BMP proteins, which had already been described for hyaluronic acid would have been obvious to one of ordinary skill in the art.

Valle discloses hyaluronie acid esters and their potential uses, including intraarticular injections. Abstract, cols. 1-2. Valle discloses parital or complete esters of hyaluronic acid with aliphatic, araliphatic and other alcohols, such esters being described as possessing, interesting and precious bioplastic and pharmaceutical properties and usable in innumerable fields, including cometics, surgery and medicine. Cols. 2-3, lines 64-5. Valle additionally discloses that the new products, i.e. the hyaluronic acid esters, possess the same or similar physical-chemical, pharmacological and therapeutic properties as hyaluronic acid, but are considerably more stable against degradation and further discloses a first group of esters as substances useful in therapy and other fields in which the qualities of hyaluronic acid itself dominate and may be exploited. Col. 3. Valle further discloses solubility properties of various esters, for example that the esters are soluble to a certain degree in DMSO. Col. 3, lines 8-18. Valle further discloses partial and total esters and their use as vehicles for active pharmaceutical substances and a further discussion of their solubility characteristics, which are dependent upon the degree of esterification. See entire patent. Moreover, Valle discloses that it is possible therefore on the one hand to prepare

esters of hyaluronic acid with therapeutically inacitive alcohols for use in typical indications of hyaluronic acid itself, such as for intra-articualr injections and that a considerable prolonged action due to improved stability and a retard action is disclosed, aw well as their use as vehicle and medicaments containing a pharmaceutically active substance and a hyaluronic acid ester. Col. 9, cols. 11-13. Valle also discloses the use of epidermal growth factor, another sort of growth factor than osteogenic proteins. Further it is quite understandable in view of the huge number of substances that can be combined with hyaluronic esters to form a medicament, that not every substance or type of substance can or will be mentioned. Valle also discles that partial esters with at least 5 and at most 90% of carboxylic groups esterified are of particular interest, and especially those with an esterified percentage between 50 and 80% are preferred, and also discloses 100% esterification. Col. 9.

However, mentioning a growth factor is an important hint to other similar substances especially in view of the document cited above and in view of known uses of hyaluronic acid as a carrier for osteogenic proteins, thus, it would have been obvious to a person of ordinary skill in the art at the time of the invention to combine ostegenic proteins, including BMP1-12, to from a medicament, since it was already know that a prolonged persistency of a medicament containing hyaluronic acid and a growth factor, such as BMP is desirable for effective bone formation (WO 97/32591), and the information about the retardant effect of hyaluronic acid esters make it obvious to one of skill in the art to combine growth factors like osteogenic proteins with hyaluronic acid esters. It also would have been obvious to one of ordinary skill in the art to have utilized

esters within the taught preferred ranges of Valle because they are taught to be of particular interest for the same types of uses.

Radomsky discloses a composition for treatment of bone comprising a mixture of a growth factor (including BMP1 to 12 and GDF 1 to 12 among others), which are injectable since a solution of the components and injection are contemplated, the solution (aqueous or organic) having a viscosity, which allows it to be injectable through a syringe or catheter. Abstract, cols. 1-2. The examples show compositions which further contain substances like sucrose and sodium citrate, which according to Applicants' Specification (pg. 4, lines 35-36 are considered as pore formers. The examiner notes that sodium bicarbonate and polyethylene glycol are also well known pore formers.[1] Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to have included these well known pore formers in a very similar composition as Applicants as hyaluronic acid is very similar to hyaluronic acid esters and has the benefits set forth above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer I. Harle whose telephone number is (571) 272-2763. The examiner can normally be reached on Monday through Thursday, 6:30 am to 5:00 pm,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

[1] See, e.g., US 5,5245,148, US 6,709678 – col. 9, lines 32-35, US 6,670,293, col. 1, lines 61-67, US 6,599,516, col. 2, lines 22-33.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer I. Harle
Examiner
Art Unit 1654

May 8, 2006